Patients and fluids in motion

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9

Patients and fluids in motion

Subfertility is defined as the inability to conceive after at least a year of regular unprotected sexual intercourse. The prevalence of subfertility is around 16%, affecting one out of six couples. The evaluation of couples consulting a gynecologist starts with a thorough medical history and physical examination, followed by the assessment of ovulation and semen analysis. Assessment of tubal patency is usually reserved as last test in this evaluation. The evaluation of tubal patency is an essential part of the fertility work-up, as tubal disease accounts for 11-30% of subfertility. To evaluate tubal patency, various tests are available, including hysterosalpingography (HSG), diagnostic laparoscopy with dye test and hysterosalpingo sonography (HyCoSy or HyFoSy). The diagnosis idiopathic (or unexplained) subfertility is made if the fertility work-up failed to find a cause for the subfertility, thus the evaluation demonstrated a regular ovulation, normal semen quality and patent Fallopian tubes. Following the Dutch guideline, the first step in treatment for idiopathic subfertility is intrauterine insemination (IUI) if the predicted likelihood of spontaneous conception within 12 months after tubal testing is 30% or lower, based on the prognostic model of Hunault. IUI, commonly combined with ovarian stimulation, is a relatively simple procedure in which semen is 'washed' in the laboratory and inserted into the uterine cavity at the time of ovulation, using a small catheter. If IUI is unsuccessful, in vitro fertilization (IVF) is offered to couples with idiopathic subfertility, based upon the concept that IVF bypasses unknown pathology in the process of spontaneous conception.

The work presented in the studies of this thesis evaluated different aspects of diagnostics and therapeutic interventions in idiopathic subfertility. The first part explored the therapeutic effect of HSG. The second part introduced the evaluation of fallopian tubes by HyFoSy as part of the fertility work-up. The third part compared immobilization and immediate mobilization after IUI in terms of ongoing pregnancies.

Chapter 1 gives an outline and describes the objectives of this thesis. The aim of this thesis was to answer the following questions:

1. Does tubal flushing during HSG, as part of the basic fertility work-up, with an oil-based contrast medium leads to higher ongoing pregnancy rates within six months compared to the use of water-based contrast medium?
2. Can we identify patient characteristics that distinguish which ovulatory subfertile women undergoing HSG benefit more or less from tubal flushing with oil-based contrast medium compared to water-based contrast medium?
3. What is the cost-effectiveness of tubal flushing during HSG, as part of the fertility work-up, using an oil-based contrast medium compared with a water-based contrast medium?
4. What are the long term reproductive outcomes of the use of oil-based or water-based contrast at HSG?

5. Is HyFoSy a cost-effective alternative for HSG in assessing tubal patency in subfertile women in terms of ongoing pregnancies?
6. Does 15 minutes of immobilisation after IUI improve pregnancy rates in subfertile couples?

PART I Therapeutic effects of diagnostic patency testing by HSG

Pregnancy rates among subfertile women had been reported to increase following HSG, but it was unclear whether the type of contrast medium used (oil-based or water-based) influences this potential therapeutic effect.

Chapter 2 describes a large multicenter trial comparing the ongoing pregnancy rate following the use of oil-based contrast with water-based contrast at HSG for a period of six months, the H2Oil trial. 1,119 subfertile women were randomly assigned to HSG with oil-based contrast (557) or water-based contrast (562). Subsequently, couples received expectant management or underwent IUI based on the outcomes of the prognostic model of Hunault. In case of bilateral tubal occlusion, patients were referred to IVF. The results showed that the ongoing pregnancy rate within 6 months after randomization was significantly higher among subfertile women who underwent HSG with oil-based contrast compared to the use of water contrast ((220/554 (39.7%) in the oil-group versus 161/554 (29.1%) in the water-group (relative risk [RR] 1.37; 95% confidence interval [CI] 1.16-1.61)). The subsequent live birth rates were also significantly higher after the use of oil-based contrast compared to water-based contrast (214/552 (38.8%) versus 155/552 (28.1%), respectively (RR 1.38; 95% CI 1.17-1.64)).

Chapter 3 evaluates if we could identify patient characteristics that distinguish which ovulatory subfertile women undergoing HSG benefit more or less from flushing with oil-based contrast medium compared to water-based contrast medium, using the data from the H2Oil trial. We built logistic regression models to predict ongoing pregnancy and live birth (secondary outcome) as a function of the specific contrast, the specific marker and marker-by-contrast-interaction. Among the studied baseline characteristics, BMI (p=0.002) and semen volume (p=0.02) were statistically significant prognosticators. The treatment effect of oil-based contrast was stronger in women with a BMI ≤30 kg/m^2 (RR 1.54; 95% CI 1.23-1.92, p=0.002), and in women whose partner had a semen volume >3mL (RR 1.77; 95% CI 1.28-2.46, p=0.02). The presence of a treatment effect is not related to characteristics of the couple, although lean women, women whose partner has a large semen volume and possibly smokers might benefit more from the use of oil-based contrast. All subfertile, ovulatory women younger than 39 years of age with a low risk for tubal pathology will benefit from an HSG with oil-based contrast.

Chapter 4 describes the economic evaluation of the H2Oil trial. We compared the direct medical costs of the contrast media intervention, subfertility treatments, and miscarriage

within 6 months of randomization for the primary outcome of ongoing pregnancy. All calculations were standardized to 2017 prices using U.S. consumer price index data. For the primary outcome measure, the mean costs per couple were $US 2,014 in the oil-group and $US 1,144 in the water-group, with a corresponding ICER of $US 8,198 per additional ongoing pregnancy. For live birth, the mean costs per couple were $US 11,532 in the oil-group and $US 8,310 in the water-group, with a corresponding ICER of $US 30,112 per additional live birth. If society is willing to pay $US 8,198 for an additional ongoing pregnancy, HSG with oil-based contrast is a cost-effective strategy compared to HSG with water-based contrast for subfertile, ovulatory women at low risk for tubal pathology.

Chapter 5 presents the long-term reproductive outcomes of the H2Oil trial. Data regarding fertility treatments and pregnancies were obtained from the electronic medical records of the H2Oil trial participants. In addition to these data, all H2Oil participants were approached, after signing an informed consent, to fill in a questionnaire regarding pregnancies and fertility treatments. The results showed a significant higher ongoing pregnancy rate after an HSG with oil-based contrast compared to an HSG with water-based contrast over a period of 5 years (444/555 (80.0%) in the oil-group versus 419/559 (75.0%) in the water-group (RR 1.07; 95% CI 1.00-1.14, P=0.04)). The subsequent live birth rates were also significant higher after the use of oil-based contrast compared to water-based contrast (415/555 (74.8%) in the oil-group versus 376/559 (67.3%) in the water-group (RR 1.11; 95%CI 1.03-1.20, P=0.006)). Furthermore, the time to ongoing pregnancy was significantly shorter and more pregnancies were spontaneously conceived after an HSG with oil-based contrast.

PART II Tubal patency testing: HyFoSy as alternative for HSG

Traditionally, tubal patency testing during fertility work-up is performed by HSG. Hysterosalpingo-foam sonography (HyFoSy) is an alternative technique to HSG that is thought to have comparable accuracy as HSG, while it is less expensive and more patient friendly.

Chapter 6 describes the study protocol for the evaluation of the effectiveness and costs of management guided by HyFoSy or by HSG. The study design is a multicenter prospective comparative study with a randomized controlled trial design. Patients between 18 and 41 years old, who are scheduled for tubal patency testing as part of the fertility work-up will be assessed for eligibility. Women with anovulatory cycles not responding on ovulation induction, endometriosis, severe male factor (Total motile sperm count $<1x10^6$/ml) or a known contrast (iodine) allergy will be excluded. Consenting participants will be scheduled for both HyFoSy and HSG in a random order. If the results of both tubal patency tests are concordant, the planned fertility treatment is based on the test results in accordance with the current Dutch guideline. Participants in whom the

results of HyFoSy and HSG are discordant are subsequently included in a randomized trial in which they will be randomized between management based on the results of HyFoSy or management based on the results of HSG. The planned fertility treatment is based on the test results in accordance with the current Dutch guideline. The primary outcome for the comparison of the two strategies is ongoing pregnancy leading to live birth within 12 months after inclusion. Secondary outcomes are pain scores after tubal testing, time to pregnancy, clinical pregnancy, miscarriage, multiple pregnancy, preterm birth, quality of life and absence of work. In addition, an economic evaluation alongside this randomized controlled trial will be conducted after completion of the trial (September 2020).

PART III (Im)mobilization after Intrauterine insemination

In case the fertility work-up showed no cause for the subfertility, the first step in treatment for idiopathic subfertility is IUI. Prior RCTs reported a beneficial effect of supine immobilization for 15 minutes following IUI compared to immediate mobilization. However, these studies could be criticized and the underlying fertility enhancing mechanism remained unclear.

Chapter 7 presents the results of a large single center randomized controlled trial. A total of 244 participants were randomly assigned for 15 minutes of immobilization and 254 participants to direct mobilization after IUI for a maximum of six cycles. The ongoing pregnancy rate per couple was not found to be superior in the immobilization group (76/236 in the immobilization group versus 98/245 in the mobilization group, one-sided p-value=0.97 (RR 0.81; 95% CI 0.63-1.02, risk difference: -7.8%, 95% CI -16.4%-0.8%). No difference was found in miscarriage rate, multiple gestation rate, live birth rate and time to pregnancy between the groups. We concluded that a possible beneficial effect of supine immobilization after IUI is at least doubtful and straightforward implementation does not seem to be justified.

Chapter 8 contains a general discussion of this thesis and the implications for future research and clinical practice.

The answers to the research questions are as follows:

1. Does tubal flushing during HSG, as part of the basic fertility work-up, with an oil-based contrast medium leads to higher ongoing pregnancy rates within six months compared to the use of water-based contrast medium?

Tubal flushing during HSG with oil-based contrast leads to 10% more ongoing pregnancies as well as life births compared to an HSG with water-based contrast within six months after randomization.

2. Can we identify patient characteristics that distinguish which ovulatory subfertile women undergoing HSG benefit more or less from flushing with oil-based contrast medium compared to water-based contrast medium?

HSG with oil-based contrast medium results in higher 6-month ongoing pregnancy and live birth rates as compared to HSG with water-based contrast medium and this treatment effect is independent of characteristics of the couple.

3. What is the cost-effectiveness of tubal flushing using an oil-based contrast medium compared with a water-based contrast medium?

If society is willing to pay $US 8,198 for an additional ongoing pregnancy, HSG with oil-based contrast is a cost-effective strategy compared to HSG with water-based contrast for subfertile, ovulatory women at low risk for tubal pathology. The difference in costs are mainly originated from the higher market price of the oil-based contrast. If the difference in costs of the contrast media decreases, flushing with oil-based contrast will be more cost-effective.

4. What is the long term reproductive outcome of the use of oil-based or water-based contrast at HSG?

An HSG with oil-based contrast results in a higher ongoing pregnancy rate, a higher live birth rate, more pregnancies spontaneously conceived and a shorter time to pregnancy compared to an HSG with water-based over a 5-year period.

5. Is HyFoSy a cost-effective alternative for HSG in assessing tubal patency in subfertile women in terms of ongoing pregnancies?

The results of the protocol described in this thesis will address this question.

6. Does 15 minutes of immobilisation after IUI improve pregnancy rates in subfertile couples?

Immobilisation for 15 minutes after IUI does not improve pregnancy rates compared to immediate mobilisation.